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THE PHYSICIAN AND THE PROBLEM OF ALCOHOLISM*

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WHAT I shall have to say this afternoon on alcoholism is directed not at all to the specialist treating this disease but to the non-specialist, the physician who meets the alcoholic and his family as incidental to his practice of medicine. The practitioner cannot usually be expected to treat the alcohol habit competently, nor would he, as a rule, wish to attempt this treatment. But nevertheless the part he plays toward the success or failure of eventual recovery of the alcoholic is often the crucial part. It is to the physician that the problems of the alcoholic and his family are usually brought first. It is the attitude of the physician which, in great measure, determines the course which the alcoholic will follow and also the understanding and coöperation—or lack of them—which the alcoholic and his family will show. A great many former alcoholics, who today occupy important and respected positions in our society, owe their eventual rehabilitation to the competent primary guidance of their physicians. There are, I am sorry to say, many, probably a great many more alcoholics who did not rece good primary guidance and for whom their physicians were not but actual, and sometimes insurmountable, obstacles to recovery. We

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usually think of that basic Hippocratic aphorism of our profession, *prima non nocere*–first do no harm–as applying only to misuse of drug and knife, but in respect to alcoholism the misuse of word and attitude may be equally harmful.

I shall devote much of my talk to this matter of the attitude of the physician toward the alcoholic and the influence of this attitude upon the treatment for alcoholism. But first, I want to try to clarify a common misunderstanding which has frequently influenced the scientific if not the personal attitude of the physician toward the alcoholic and his problem. It is the misconception of alcoholic as contrasted to alcoholism; one concerns the man and the other his habit. I have said that the non-specialist practitioner cannot usually be expected to treat alcoholism; he can, however, most competently treat the alcoholic. This is not a quibble in terminology; there is a vast difference between the two which is frequently overlooked. The treatment of the alcoholic consists in sobering up the man, giving him some symptomatic relief, determining and remedying his physical disturbances, correcting his dietary deficiencies, keeping him under good medical and hygienic care until some measure of normal physical health is restored. Unfortunately, some physicians, and even some institutions, consider this an ultimate treatment. Under their care the alcoholic, in a week or a month, may show marked physical improvement; he may even stop drinking for another week or another month but in the great majority of instances he starts his heavy drinking again. This relapse and a second, a third, a fourth and a fifth, each following a period of treatment of the alcoholic, are discouraging. It leads to pessimism not only as to the expectation of more than temporary benefits of physical rehabilitation but also, and more important, as to the probability of any recovery from alcoholism. The pessimism shows in the attitude of the physician toward the alcoholic; it is sensed acutely by him to the detriment of any subsequent therapeutic success.

Actually the pessimism is not justified. It is not surprising or discouraging that a habit persists when treatment is not directed to the habit but only to the physical derangements which are results and not causes of the habit.

Again, the pessimism of the physician may originate in or be reinforced by two undeniable facts which seem discouraging in their baldest statement but which are far from discouraging in their interpreta-

tion. The first is that alcoholism cannot be cured. That, today, in the great majority of instances, is scientifically correct. But it is correct only if the physician will insist upon the same rigid definition and use of the word "cure" when applied to other diseases. There is no specific for alcoholism as there is for syphilis. Likewise, there is none for tuberculosis and typhoid fever, but this lack does not impart a corresponding pessimism as to a possible recovery. The fact that there is no cure, in the strictest sense of the word, for these diseases does not deter the physician from applying every measure which will give the greatest opportunity for recovery. We are prone to forget that the tremendous advancement of medicine which arouses our enthusiasm has by no means taken all of the truth from the modest words—now 400 years old—of Paré: "I treated him; God healed him." Or perhaps you might prefer to say it impersonally, but with equal medical humility and understanding: "He got well under treatment."

The second undeniable fact is that recovery from alcoholism nearly always means only that the former alcoholic has ceased to drink and, of course, has become rehabilitated. It rarely means that he has regained or obtained what might be called a normal reaction to the use of alcohol. The compulsion to drink excessively is not eradicated, it is simply brought under control and it is held under control but only as long as no alcohol is taken. One drink, and the compulsion may again dominate. Recovery from the habit is usually a symptomatic recovery only.

These two facts must be recognized and they must be faced not only by the patient but also by his physician. They are not discouraging facts that can be construed to give to the physician—and through him to the patient—the obstacle of disbelief in recovery. The important fact is that with proper guidance a high percentage of alcoholics can learn to control their habit and become rehabilitated. And most of them are—even aside from any humanitarian consideration—well worth rehabilitating.

There are many forms of treatment for alcoholism and, for all, recoveries are claimed and no doubt obtained. Multitherapy always arouses suspicion in the mind of the physician, for from experience he knows that any malady which has many treatments has no good one. But the assumption that because there are many treatments with recoveries from alcoholism, none is valid must rest upon *a priori* assumption that the excessive use of alcohol, the determining symptom,

has always a common etiology. I do not think that it can be shown that there is a common etiology for excessive drinking.

Such a statement implies disbelief in physical, chemical, or pharmacological idiosyncrasy as the basis upon which excessive drinking rests. The discovery of such a basis, if one could ever be made, would hold out great promise not only for the pharmacological cure of alcoholism but also for the more important prevention by the designation, from tests, of those who were susceptible to alcoholism and therefore must never drink. The psychiatrist, from his inability to find a definite prealcoholic type of personality, is prone at times to pass the matter back to the physiologist and pharmacologist. It is true that he raises pertinent questions, such as these: Some men with manic depressive psychosis drink to excess, especially periodically, but others with this psychosis do not. Why, when alcohol is universally available and widely experienced, do some find a partial symptomatic relief in drinking and others do not? The same applies to the early schizophrenic. Some become violent symptomatic drinkers; others do not drink at all. Among alcoholics there appears to be a large number of psychoneurotics; but there is a vastly larger number of psychoneurotics of equal or even greater involvement who, with like opportunity, do not drink to excess. Such facts as these quite naturally suggest the possibility of a somatic common denominator acting among those who turn to alcohol. None which is valid has ever been found, and in the extensive physiological studies dealing with the action of alcohol none has ever been soundly indicated.

One especial feature characterizing the drinking behavior of many alcoholics has led some authors to the postulation of an allergic-like reaction to alcohol which, by them, is taken as a common denominating somatic factor. This so-called allergy has as its major manifestation not the usual allergic reactions, but instead, uncontrollable drinking after a drink is taken. That is, the alcoholic can become abstinent and can remain so but he cannot become moderate in his use of alcohol. His action is none, or all.

The conception of an allergic-like response to alcohol has had a measure of recent popularity because it is particularly acceptable to the alcoholic: First, in view of the wide popular interest in allergies for foods and pollens, the alcoholic can find an understandable explanation of why he must shun all alcohol; second, the allergy idea pro-

vides the alcoholic with an excuse which receives sympathetic understanding when he refuses a drink with the explanation that he is "allergic" to alcohol; and third, he is given an ego satisfaction, which he needs badly, in being physically rather than mentally or morally different from the majority of human beings and in having no volitional responsibility for this difference. The acute sufferer from asthma, hives and hay fever rarely appreciates the distinction conferred by his allergy, but the individual who, after taking one drink, invariably goes on a spree may find considerable comfort in the explanation that his behavior is due to an unfortunate body chemistry.

Now, as a matter of fact, when the literature is searched carefully to follow the rise of the concept of an allergic origin of craving it is found that with few exceptions the idea advanced has been mainly metaphorical. The actual term used has been "psychic allergy" or a "psychobiological sensitivity which is practically an allergy" which perhaps may be defined as a condition of exaggerated response in which the allergen is a mental or emotional state. It is doubtful if the readers of such statements–and certainly not the patient to whom they are repeated–note the qualifying term of psychic, psychic allergy, which removes the matter from somatic cellular reactions and restores it to mental reactions. The more familiar ideas of chemical allergy to foods and pollens tend to blind one to the qualification of "psychic allergy" and lead to the inference of a true chemical allergy to alcohol for which there is no scientific basis.

The attempt to express alcoholism in terms of allergy is not surprising in light of the long history of the effort to find a pharmacological basis. Similar attempt has been made to attach the basis of alcoholism to many medical discoveries which have attracted wide popular interest. Thus, near the end of the last century attempts were made to prepare an immunizing serum from gradually alcoholized horses. Toxic states, gouty impurities, and endocrine disturbances have all been advanced as causes. Such attempts have not failed because they advanced a single etiology or a somatic etiology, but because they advanced false etiologies.

The lack of a defined common etiology means that the practitioner, in dealing with his alcoholic patient, must make some differentiations if he is to direct his patient to the most advantageous therapy–the one best suited to the alcoholic. At this early stage there comes an im-

portant qualification; it is the one of economics. If the patient can afford possibly long and necessarily expensive care, the diagnosis and full responsibility for therapy and rehabilitation can be shifted to one of the competently staffed private institutions treating alcoholism (in contrast to those treating only the alcoholic as I developed earlier). In many, perhaps the majority of instances, the alcoholic cannot afford this care. The responsibility of obtaining the most advantageous therapy that the patient can afford then rests upon the physician. The selection of the therapy involves preliminary diagnostic study but of a sort that requires no extensive psychiatric sophistication. The questions before the physician are: First, is this patient an alcoholic? And second, if so, what general sort of alcoholic is he?

The first question enters only occasionally. Usually the history of the individual leaves little doubt that he is drinking in great excess but occasionally there is doubt. Once in a while an individual who is distinctly hypochrondriacal will volunteer the statement that he fears alcohol is getting the better of him and that he is becoming an alcoholic. More often perhaps the wife or the mother comes to the practitioner with the statement—based often on a complete lack of sophistication or, more likely, on strong anti-alcohol convictions—that her husband or son is an alcoholic. Such statements are frequently expressions of a losing part in an argument on the question of any use of alcohol, in which reinforcement from the physician is sought.

The presumed alcoholic, brought or forced to the physician by a member of his family is, as a rule, not in a favorable situation for that rapport between the physician and patient which is necessary for the successful treatment of alcoholism. Somewhat more favorably situated is the patient who is under treatment for some somatic complaint and in whom the physician discovers the probability of alcoholism. Both such patients may stoutly deny that they are alcoholics. It would seem undesirable that the physician make his decision wholly on the basis of the amount of alcohol consumed per day unless that amount is so large as to be unmistakably excessive even under the most liberal standards. I have heard physicians discuss the matter of amounts of drinking that indicate alcoholism and these amounts vary only with the physician's personal convictions and habits and hopes. Thus I have heard physicians say that they considered as an alcoholic anyone who daily drank two glasses of beer or two ounces of whisky; and I have

heard others dismiss with a shrug the drinking of a pint or more of whisky a day, over a long period of time.

Again, it may be well to remember that in stating amounts consumed daily, both the alcoholic and his family are often biased and consciously or unconsciously over- or under-estimate. One of the best tests for many, but not all, alcoholics is not in amount, not in asking the possible alcoholic to see if he can abstain entirely—for many can—but to limit his drinking for a time strictly to two drinks a day. That, most cannot do. And the fact that he cannot, may, for the first time, bring home to the patient the fact that he is actually an alcoholic and does not have the control over his habit which he believed he had.

Having established the fact, or presumption, that the patient is an alcoholic, the next diagnostic measure—barring the physical examination—would be to make an evaluation as to what sort of alcoholic the patient is. There are numerous and elaborate classifications but a convenient and sufficient, but quite arbitrary one, for the general purposes with which I deal is: (1) symptomatic drinking; (2) true addiction; and (3) secondary addiction. The distinctions are, as I say, arbitrary and open to psychiatric argument which I certainly would not attempt to defend. But for the purposes here, I think it may be taken that the symptomatic drinker is a man whose excessive drinking is one of many possible symptoms of some deep-seated disturbance—possibly a psychosis. Some diagnostic guidance may be had from the nature of the drinking. If it is periodic, perhaps at intervals of several months, with abstemious periods, the possibility of a manic depressive psychosis in which the patient drinks in either the manic or depressive stage may suggest itself; likewise suggested may be epileptic states; and occasionally severe endocrine dysfunction. If symptomatic drinking is steady, wild and witless, the possibility of early schizophrenia (especially if the patient is young) or early general paresis, may be suggested. Recovery from alcoholism under any form of treatment directed only at the alcoholism is useless in the symptomatic drinker. Psychotherapy, aversion therapy, or counselling by Alcoholics Anonymous would lead only to failure with the possible reinforcement of the pessimistic idea that treatment for alcoholism is hopeless. Thorough psychiatric examination is indicated before any time is wasted in treating the habit of the symptomatic drinker.

In most classifications, a distinction is made between so-called true

addicts and secondary addicts. The distinction is mainly that of degree of psychopathology inherent in the drinker before he started drinking. The true addicts have a profound but non-psychotic maladjustment; they are the most dramatic and the most pitiful of the excessive drinkers but fortunately, at present, the smallest group. I put in the qualification of "at present," for a profound and widespread alteration of social and economic conditions may lower the level at which maladjustment of personality is manifest. The true addicts make up the group that occupies a prominent position in popular and medical views, because they express to the highest degree the general conception of the true alcoholics—the men to whom alcohol is a complete solution to the problem of adjustment. They do not respond well to treatment, but they are not entirely hopeless, for if they can be shown and convinced that their conflicts can be relieved by means other than alcohol, they may develop more acceptable behavior. They, again, are not the type of alcoholics for whom the aversion treatment or the counselling of the Alcoholics Anonymous, or any treatment on a similar plane, would be likely of success. They are the problems, and the difficult problems, for the psychotherapist in the broadest use of this term.

So far, I have tried to differentiate two broad classes—I might say exclude them—on the basis of maladjustment so severe that abolition only of the symptoms of excessive drinking and rehabilitation would yield an individual who was still unable to make adjustments even approaching the normal. After this exclusion, there is left a very large number of alcoholics whose prealcoholic psychopathology falls within that wide and indefinite range for individuals who could make reasonably normal adjustments. They were not, before their alcoholism developed, severe psychoneurotics; they are men whose drinking habits have become abnormal under the influence of predominantly exogenous factors—including alcohol itself.

No prealcoholic personality type has been differentiated for this large group of alcoholics to which I have reference here. Possibly searching psychiatric examination might indicate certain tendencies but as yet none has been found which is sufficient for the selection, with any certainty, of potential alcoholics of this group. After the alcoholism has become well developed, however, certain general personality or character traits seem to appear, to be superimposed or possibly uncovered. They are certainly not to be taken as diagnostic criteria, for

they may be found in many non-alcoholics, but they do serve in a measure as a fairly common factor among alcoholics. The importance of this factor lies in the fact that it gives some understanding of the behavior of the alcoholic. It therefore indicates an approach to dealing with the alcoholic; it indicates the attitude of the physician particularly toward establishing that rapport which is the first and most essential feature toward any successful therapy for the alcoholism of the so-called secondary addict.

It is not within my competence, nor is it of practical interest to the practitioner, to attempt any analysis of the basic forces operating to bring about the changes in the personality or character of the alcoholic. It is the clinical pictures only in which I am interested here. In its exhibition the change is one toward the essential egocentricity that so strongly characterizes the child. The alcoholic may be thought of as a child and may best be handled as a child. An appearance of grave respect, deep understanding, and broad tolerance with no recriminations, illicits confidence from the child—and from the alcoholic.

The development of the apparent retrogressive change in personality or character of the alcoholic is often slow. In the early stages of excessive drinking it is difficult to detect the beginning alcoholic from the occasional heavy drinkers who do not become alcoholics. In the face of difficulties the incipient alcoholic tends, perhaps, to drink more often than his associates and his drinking is more likely to reach the stage of drunkenness. As he drinks more, he develops a greater psychological tolerance to alcohol and large amounts may be required to give gratification. Eventually, as a possible turning point, he goes on his first spree of completely uncontrolled drinking. At first, sprees may be only occasional, but they tend to become more frequent, to occur from less and less provocation and to last longer. Gradually a compulsion to drink is developed; a spree tends to follow any drinking but periods of abstinence may still occur between sprees. At this stage, after the spree, a deflated feeling is experienced; the enthusiasm and exuberance which were carried into earlier sprees and the vigor which was carried out of them is lacking. The alcoholic is tired, guilty, contrite, and, in his remorse, makes vows. But with the first subsequent drink, all responsibility to vows is disregarded. And preliminary to that drink, there is frequently a fairly definite prodromal syndrome. A psychic tension develops; the alcoholic is irritable, cranky, sour,

restless and jittery. Only a drink will relieve this tension—and a drink means a spree.

At this stage there is usually evidence of a type of thinking that shows, undisguised, the alcoholic's juvenile egocentricity. He feels omnipotent but insecure. He demands, and expects, that he shall be the center of interest. He is sorry for himself and interprets even the most reasonable demands as thwarting him. He wants to dominate. He objects to routine and restraint. His attitude may anticipate thwarting and be hostile, cynical, defiant. At the same time he may exhibit for art, or beauty, or music, enthusiasms that are as exaggerated and unguided as those of a "bobby sock" crooner fan. He senses a loneliness and isolation, a feeling of being apart and of the impossibility of being close to others. To this he may over-react into complete isolation or, in contrast, to a fawning effort to ingratiate. He promises to do better—he has learned his lesson—but his words carry only the responsibility of those of the temporarily frightened and contrite spoiled child. In degrees greater or less, exhibited through the superficialities of a culture which is polished or crude, this is the patient with whom the practitioner must deal.

If the attitude of the physician is understanding, tolerant, patient, serious, he may win the confidence of his patient and be able to help him. Recriminations are useless, for the alcoholic has deep within him the strongest feelings of guilt and responds to them with hostility. They are only further proof that no one understands him. A high moral tone, preaching, drives him away. The gift of really understanding the alcoholic, winning his confidence and coöperation, is often held in high degree by ex-alcoholics who act as lay therapists or group therapists as in Alcoholics Anonymous. They have been through the same experience themselves; they know the feeling of tension, of discontent, of omnipotence, of guilt, and of resentment. They know, and forgive, the inevitable "slips;" after the spree, they are able to maintain their fully understanding attitude and an unabated confidence. The physician, to be succesful, must maintain the same confidence.

There is no group of individuals—except children—who are more responsive to the attitude of the physician and sense his sincerity or lack of it more acutely than do alcoholics. And, as I said in the beginning of this talk, it is the attitude of the physician and his depth

of understanding which may be the deciding factor in the recovery of the alcoholic; if he understands him and if he can make the members of the family and business associates likewise understand and cooperate, he has a good chance of steering the alcoholic toward recovery. Contrariwise, an adverse attitude, whatever its reason, may be, and may remain, the insurmountable obstacle to recovery.

I have also mentioned earlier that there are many different therapies of alcoholism. They are seemingly widely divergent in nature, but they have one element in common. It is the essential conviction of the possibility of recovery. The alcoholic will rarely recover under any treatment unless he believes he can recover and he wants to recover. One might go even further and say that if he can be so inspired to believe in recovery, he will recover under almost any kind of treatment if his confidence is carried over to the treatment and identified with it. It is, I think, the major function of the practitioner to inspire the desire and confidence and then select, at the necessary economic level, a therapy which he believes will be most suited to hold the respect of the patient.

In a recent article, Dr. Abraham Myerson has summed up the essential approach to successful therapy and also gives expression to a somewhat pessimistic view as to the specific virtue of any one particular method of treatment. He says: "The one common factor of all the therapeutics of alcohol addiction is embodied in the statement which is made by all therapists. *The patient must have the desire to be treated. He must wish to get well. He must be willing to cooperate.*" To these factors I should add the one which I have just discussed and which I think is equally important: *He must believe that he can get well.* Again, in this last respect the lay therapist who is an ex-alcoholic has a particular advantage; he not only speaks the alcoholic's language and knows his feelings, but he has been through it all himself and is there as a tangible example of the possibility of recovery.

In creating the will to recover, it is usually essential to bear continually in mind the predominantly egocentric attitude of the alcoholic. The reason for recovery had best be made to stem from his own self-interests, his own ego, and not from family neglect and failure of duties which are topics prone to arouse undesirable emotional reactions. Something of this reaction, but in a most desirable direction, can sometimes be transferred to the alcohol itself by bringing it into

competition with his ego. He may believe, or pretend to believe, that he has control over his drinking; he is the master. If he can be made to see, and made to realize that others also see, that in reality he is not the master, that, in spite of his claimed omnipotence, he is the servant, his egocentricity may be turned to advantage as resentment against the alcohol, or as a fear of it. Again, a serious and dispassionate explanation by the physician of the probability of fairly rapid somatic deterioration as incidental to his heavy drinking, may arouse sufficient fear and yet provide an acceptable excuse for the desire to stop drinking.

Dr. Myerson, after stating the essential prerequisites to any successful therapy that I have given above, expands, as I have said, upon his doubts as to the specificity of any particular method. He says: "It may be that whatever method is used, if this will is present, if the desire to be free of alcohol addiction has reached that point of burning heat which James calls 'conversion,' it does not matter much whether benzedrine sulfate, which makes one feel good, or wine of ipecac, which makes one vomit, is utilized; it is of relatively little importance whether an exhorter does the trick by firing zeal through the fear of God or the friendly greeter of Alcoholics Anonymous is the agent of reform. The alkaloid strychnine will work as well, and no better, than the hormone insulin. In other words, the essential of all these therapeutic measures seems to be to enlist the cooperation of the patient, to galvanize his will, to bring about his conversion rather than to use any one specific measure."

What Dr. Myerson, as a psychiatrist, is saying, if I might rephrase his words in these possibly blunter ones of a physiologist, is: the therapy of alcoholism is faith healing. The same, with equal bluntness, might be said of a good deal of psychotherapy. But even if it be true, I see no implication of belittlement. Physicians are prone to give a bad name to the whole conception of faith healing because they have come to regard this term in derogation from the early and even modern misapplication of this therapy to somatic diseases. Certainly the treatment of tuberculosis and broken legs by the laying on of hands and prayer deserves derision. But I do not think this derision should be inherent in the term "faith healing" when applied to the alteration of behavior habits. I doubt extremely whether faith has ever moved any mountains, but I know beyond doubt that it has moved

and is moving whole nations of men into patterns of behavior, into habits for the maintenance of which they are willing to die. I see nothing to be ashamed of in the statement that much of the therapy of alcoholism is faith healing and interpreting the rapport established between the patient and therapist as a feature common to all faith healing. All that these statements signify is that there is no specific somatic–pharmacologic–therapy for alcoholism. The important fact is that a great many alcoholics can be helped to recovery and to full rehabilitation.

While I am not wholly in agreement, let us for the moment, to avoid argument, accept the baldest interpretation of the therapies as faith healing. And you will remember that I have excluded from the handling of alcoholism those alcoholics who are symptomatic–psychotic–drinkers and those with extensive prealcoholic psychopathology. The alcoholics to whom I am attempting to direct the attention of non-specialist practitioners are those of that group who, when their alcoholism is cured, their prealcoholic health and character restored, are, within a broad interpretation of the term, reasonably normal human beings. They constitute the largest group of alcoholics and the majority cannot afford a long period of institutional care but must be treated, so to speak, as ambulatory. We shall assume further that the practitioner has met them with a helpful attitude and carried out, with some success, his vitally important function of establishing the preliminary attitude toward treatment. The patient is thus prepared for the therapy of his alcoholism. The selection of the therapy falls upon the physician. I have assumed, wholly for our argument, that the therapy is faith healing but a common designation does not mean that all forms which the healing may take are equally suited to the particular patient. The therapy selected must be one that suits the patient, one that he can believe in and will respect.

The practitioner may decide that his patient will react best to the group fellowship of Alcoholics Anonymous; that he can be touched by proffered understanding and by actual aid in his "slips," and that he can be aroused to a deep desire and responsibility to help others. If so, the necessary contact should be made. If, on the other hand, the physician feels that his patient does not have these qualities–perhaps a trifle sentimental in nature–he might turn to the one method best suited to the patient to whom a rational medical explanation would

make the strongest appeal, the so-called aversion or conditioned-reflex treatment. This method, which consists in the attempt to arouse an actual distaste for alcoholic beverages by the association of their taste with nausea and vomiting, possibly has a sounder physiological basis than faith healing only, but for it, the preliminary rapport is necessary; during it, a certain amount of suggestions; and after it, periods of reinforcement. If this forthright therapy, which perhaps makes its greatest appeal to the practical and hard-headed patient, seems also unsuited, there remains the individual, more expensive, and longer help of the psychotherapist who should be selected not only for his interest in alcoholism, but also for his personality.

At the danger of being unwarrantedly repetitious, I want to say again that the most essential step in any therapy of alcoholism is the initial contact—the part played by the practitioner. When his approach to the alcoholic is understanding and tolerant, something of the rapport is established; and when the practitioner is willing to listen, to advise, to talk to the family and help straighten out social difficulties, to be on the alcoholic's side, to guide him but not be exploited by him, he is himself carrying out the soundest and most helpful therapy of the alcoholism itself.

I have spent much time on what I have repeatedly called the physician's attitude and in so doing I have particularized. Now I want to generalize, to consider what forces have shaped the attitudes of the physician and too often shaped them to the detriment of the alcoholic. There is sometimes a tendency on the part of the members of our profession to feel that we are not only the inspirers for any broad social changes with medical implications but also the leaders who bring them into being. Sometimes I am led to wonder if this belief is justified. We all are products of the society in which we grow up; our fundamental views and beliefs on social matters, even those with medical implications are, I suspect, most often determined before we go into medicine. It is a chastening reflection that some of the greatest humanitarian social reforms built out of the potentialities of medicine were not seen or pioneered or led to social application by the physician. Sometimes they have even been obstructed by him. Often his attitude has been as bigoted as that of his non-medical neighbors.

I might illustrate this unfortunate fact with the rise and growth, a century ago, of an idea which is very pertinent to that held today

regarding alcoholism. You will recall that about a century and a half ago, Dr. Phillipe Pinel advanced the idea that the symptoms of insanity might be ameliorated by humane care. To him, humane care meant the removal of manacles and chains and the discontinuance of torture. This therapeutic experiment aroused little interest among physicians. Half a century after his time there was no publicly supported institution in the United States for the care of the chronic insane. And, what was even more important, insanity was not considered by the physician as a disease in the sense that typhoid and smallpox were diseases. Insanity was felt to have in it a large element of plain human weakness, meanness and immorality—it was misbehavior for which the patient was, in some measure, responsible. The laws of the period made perhaps a better distinction as to responsibility than did the public and the physician. The physician, by and large, in dealing with the insane showed his impatience, his disgust, his dislike; he showed complete lack of understanding and sympathy. Probably he did not personally whip his patient, or throw cold water on him, or chain him in a cellar, but he directed and saw these things done. The deep sympathy and compassion that the physician had for the somatically ill did not flow over to the mentally ill; like the rest of the public he could find a cruel humor for their symptoms.

Then, as you will recall, in the forties of the last century, a Boston school teacher, Dorothea Linde Dix, led the crusade that resulted not only in our tax-supported care of the chronic mentally ill, but in an entire change in public attitude. The concept of mental illness, carrying with it all the compassion formerly limited only to physical illness, became the new view of the public—and of the physician as part of that public.

Today, the physician, brought up in the mores of the earlier decades of this century, holds consciously or unconsciously many of what might be called pre-Dixian ideas in regard to alcoholism. And this view tends to be intensified by these features: First, the long preaching against the use of alcohol on the basis of morals; second, and quite opposite, the moderate and controlled personal use of alcohol by the physician; and third, the cruel attitude which sees in drunkenness on street, or stage, or radio, a subject of contempt or humor. The consequence is that the physician is sometimes prone to see the alcoholic as a man who deserves punishment—hence as in the

pre-Dixian days the drunk is usually a ward of the police court and his treatment a jail sentence and repeated sentences; he is prone to see the alcoholic as a man who cannot control a habit which in less degree he indulges in himself and therefore sees him in contempt for his weakness; he is prone to see the drunk as humorous or disgusting, and not as an ill man exposed to public derision but deserving sympathy and medical aid for the correction of his alcoholism; and last, he is a little prone, again sharing the public view, to believe that alcoholism is hopeless and the alcoholic not worth rehabilitating. It is such views, derived from the public of which the physician is a part, that have too frequently shaped the medical attitude toward alcoholism.

A fundamental social need today is in the development of the public opinion that alcoholism is a disease and that the alcoholic is an ill man deserving of the sympathy and care rightfully owing to an ill man. When public opinion—and in such matters public opinion often determines medical opinion—is so shaped, we will have made not only an humanitarian advancement but one of great practical importance toward the rehabilitation of the alcoholic and the prevention of alcoholism. Organized movements are already started which have among their purposes this shaping of public opinion, not in moral, but in medical and social channels, as part of the attack on alcoholism. Among these is our group and school at the Laboratory of Applied Physiology at Yale, with its affiliated National Committee for Education in Alcoholism; the Research Council on Problems of Alcohol; and the Committee on Alcohol Hygiene stemming from Johns Hopkins Medical School.

The problem of alcoholism is, even in its strictly medical implications, a large problem. Reliable statistics indicate that in the United States today there are some fifty-five million users of alcoholic beverages. The overwhelming majority of these men and women drink in a moderation that in no way endangers them. But some two million use these beverages to an extent that renders them liable to alcoholism. It is a small percentage perhaps, but it applies to a large number. Another half million have already become alcoholics to such a degree that they have impaired their physical and mental health. Any condition that threatens the health of two million people, and has already seriously affected the health of a half million, is a public health problem of important magnitude and one deserving the respect of the physician.

RECENT ADVANCES IN THE TREATMENT OF MALARIA*

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IT WILL become increasingly important for the medical practitioner to be able to deal adequately with the malarias as increasing numbers of individuals are returned from hyperendemic malarious areas. Consequently a discussion of certain of the recent advances in the treatment of the malarias should be profitable at this time.

These improvements in therapy are not the result of the availability of new antimalarial agents, but rather are in consequence of the collection of information which permits a more rational and more effective use of those agents which are already available.

It is of general interest to note that the experimental approach that has led to these advances should be equally profitable when applied to other problems of therapy in man. In its essence, it consists of the objective appraisal of the specific effects of a chemotherapeutic agent in relation to its concentration at a given site, in this case plasma, a quantitative evaluation of the physiological factors in the host which are of importance in the determination of such a concentration and the use of these two types of information in the construction of rational regimens of therapy. This is not a new approach to problems in the field of chemotherapy. Rather, it is an extension to include the malarias, of the point of view which has facilitated the advances made in the treatment

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of bacterial diseases with the sulfonamides and penicillin. Actually the malarias in the human approximate the ideal for the application of this type of study.

A knowledge of the biology of the malarias will simplify the discussion of antimalarial agents, their uses, and their limitations. The underlying disease mechanisms have been clarified by recent work with some of the experimental avian infections[1] which appear to have somewhat similar characteristics to the human malarias. Malaria is acquired naturally when forms of the parasite known as sporozoites are introduced into the body incidental to the bites of infected anophelene mosquitoes. It seems likely that the sporozoites which are deposited locally are taken up by the tissue macrophages, whereas those which gain entrance into circulating blood, are taken up by other portions of the macrophage system of the body. Upon entry into a macrophage the sporozoite rounds up and undergoes rapid growth. This is followed by a series of segmentations, sporulations and reinvasions, which at this stage of the disease is presumably restricted to the macrophage system. This process covers a 6-7 day period, during which time the blood is devoid of demonstrable parasites.

At the end of this period certain of the tissue forms undergo another type of segmentation which results in the production of new forms of the parasite. These are capable of invading, growing and multiplying in the erythrocyte. Growth in the erythrocytes is accompanied by periodic segmentation, sporulation, and reinvasion of new erythrocytes in what is commonly called the schizogonous or asexual cycle of the plasmodium. The process continues with a progressive increase in the number of parasites in the blood until about 14 days after the day of the infection, in vivax and falciparum malaria, when a sufficient density of parasites is reached to precipitate the fever which is characteristic of clinical attack.[2a, b, d] The duration of the incubation period in quartan malaria is of somewhat uncertain duration but is usually longer than that of vivax or falciparum malaria.[2c]

The subsequent course of the untreated disease is largely conditioned by the species of the plasmodium involved in the infection, and by the presence or absence of natural and acquired immunity. In the absence of immunity, and in the absence of chemotherapeutic intervention, falciparum malaria is characterized by a short, fulminating, and not infrequently fatal course, with little tendency towards true relapses

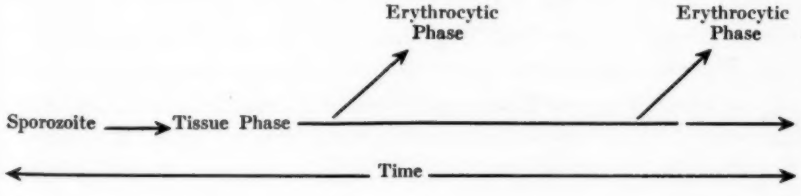
subsequent to the termination of the initial period of clinical activity.[2d] Vivax malaria is characterized by a longer initial course of clinical activity which, if untreated, frequently lasts more than 6 weeks, and by one or more relapses which may occur at intervals of a few weeks to several months.[2b] However, contrary to falciparum malaria, vivax malaria, even if untreated, almost never results in a fatal outcome in the adult. Quartan malaria is characterized by a very long period of initial clinical activity and this is followed by infrequent relapses which may occur many years after the initial clinical attack.[2c] The duration and severity of the clinical attacks in all three forms of malaria may be greatly lessened by proper treatment or modified by the presence of natural or acquired immunity.

The sexual forms of the parasite which are called gametocytes are derived from the asexual cycle of the erythrocytic phase of the disease.[2] These sexual forms are unimportant from the standpoint of the progress of the disease itself. However, they are of epidemiological importance, since they are responsible for the transmission of the disease from man to the anophelene mosquito.

It will further simplify a consideration of the problems of therapy if the mechanism of the true relapse in malaria is discussed at this time (see Figure 1). It seems likely, on the basis of our present information, that relapses in vivax malaria result from the continued presence of underlying tissue forms of the plasmodium which persist well beyond the time of the establishment of the erythrocytic forms of the parasite which is responsible for the initial clinical attack. The continued presence of these tissue forms permits subsequent sporulations, each of which may result in the re-invasion of the blood and, with the successful re-establishment of the erythrocytic forms, constitutes a discrete

FIGURE 1

MALARIA PARASITE CYCLE IN MAN



episode in the course of the disease. Should the development of immunity due to previous clinical activity be insufficient to curtail the multiplication of the new erythrocytic forms, then these may increase in number with the precipitation of renewed clinical activity characterized by both parasitemia and fever.

The normal course of falciparum malaria does not include numerous relapses as is the case with vivax malaria. This is presumably due to a lack of persisting tissue forms of the parasite very long beyond the time when the erythrocytic forms are first established. This is not to say that recurrent clinical activity within 3-4 weeks of treatment is unusual in falciparum malaria.[2d] Such early renewals of clinical activity may be attributed to therapy which is insufficient to completely interrupt the asexual cycle of the parasite in the blood, rather than to the re-invasion of the blood from persisting forms of the parasite.

Little is known of the biological characteristics of quartan malaria in terms of the probable presence or absence of such tissue forms as a necessary factor in the production of true relapses.

It is apparent, from these considerations, that the malarias are characterized by a more complex disease mechanism, insofar as the etiological agents are concerned, than is true for most bacterial diseases. This fact acquires special significance when they are considered from the standpoint of the effectiveness of the various antimalarials available for use in treatment. It must be expected in any one of the malarias that each form of the parasite has somewhat different metabolic characteristics than the others. It may be concluded from this and the fact that the different forms may reside in different cell types of the host, that they will have varying susceptibilities to chemotherapeutic agents. In confirmation of the latter belief, experience has shown that, (a) quinine, the other cinchona alkaloids, and quinacrine are highly effective against the erythrocytic asexual and sexual forms of vivax and quartan malaria and against the erythrocytic asexual forms of falciparum, (b) plasmoquin is highly effective in the usual therapeutic doses against the sexual forms (or gametocytes) of falciparum and, (c) no drug is available that has been demonstrated to possess a significant action, at well tolerated dosage, against the sporozoites or primary tissue forms of any of the three common human malarias or against the persisting tissue forms of P. vivax which are presumed to be responsible for the relapses in infections due to the latter plasmodium.

The cinchona alkaloids and quinacrine, then, are useful in the termination of clinical attacks due to any one of the three important offending plasmodia. In addition, it is to be expected that these drugs in adequate doses will produce cures in falciparum malaria, but not in vivax malaria. Further, these agents are useful in preventing clinical attacks of malaria by suppressing the development of the erythrocytic phase of each of the malarias even though they exert no effect upon the sporozoite or upon the underlying tissue phases of the plasmodium. The usefulness of plasmoquin, on the other hand would appear to be limited to the rendering of patients with falciparum malaria non-infectious by virtue of its gametocidal action. The early promise of a second use, i.e., as an anti-relapse factor in vivax malaria, has not yet been fulfilled.[3]

Quinacrine

The general usefulness of quinacrine in the control of malaria was not fully appreciated until recently. Certainly not at the time of the loss of our supply of quinine subsequent to our entry into the war.[4, 5] However, information has been developed which permits a more rational use of this important antimalarial.[6] It has been possible to translate this information into specific schedules of therapy for use in the treatment and suppression of malaria.[7] The therapeutic results with such a usage permit the conclusion that quinacrine has advantages over quinine or the other cinchona alkaloids in both the routine suppression and treatment of malaria.[8]

A discussion of the rational use of quinacrine requires the understanding that its antimalarial activity at any time is a simple reflection of its concentration in the plasma. As noted above, this is not a new concept of therapy, but a simple extension of the experience gained in the use of sulfonamides in bacterial disease to include the use of comparable agents in the treatment of malaria. However, it is not necessary to argue this point by analogy alone, since it has been established in a definitive fashion by experimental work with the human malarias.[9] A rational use of a drug in such a situation requires information on the factors which are concerned with its physiological disposition so as to clarify the relationship between drug administration and the plasma drug concentrations which are achieved and maintained on various regimens of therapy.

TABLE I

THE ABSORPTION AND EXCRETION OF QUINACRINE IN MAN

These data may be taken as typical of the results obtaining during and just after the administration of 100 mg. of quinacrine dihydrochloride three times a day to a normal adult.[6]

Day of Observation	*Daily Quinacrine mgm.*	*Plasma Concentration micrograms/L*	*Renal Excretion mgm/day*	*Fecal Excretion mgm/day*
1	300	36		
2	300	28		
3	300	32	4.8	30
4	300	48	5.5	7
5		37	7.3	36
6		17	3.3	10
7			8.0	6
8			2.2	11

TABLE II

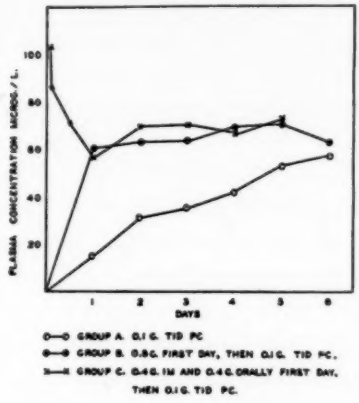
THE DISTRIBUTION OF QUINACRINE IN HUMAN BLOOD

These data may be taken as typical of the results obtaining during the administration of 100 mg. of quinacrine dihydrochloride three times a day to a normal adult.[6]

	Quinacrine Concentration (microg./liter)
Plasma	89
Plasma water	8.9
Cerebrospinal fluid	5.4
Erythrocytes	117
Leukocytes	18,400
Whole blood	551
Plasma binding (per cent total)	90

FIGURE 2

VARIOUS QUINACRINE REGIMES AND RESULTANT PLASMA CONCENTRATION



Physiological Disposition: The plasma quinacrine concentration that obtains at any time on any regimen of therapy is determined by the dosage utilized, together with the net result of the operation of the processes of absorption, distribution, degradation and excretion.[6]

It is apparent from data in Table I that quinacrine is almost completely absorbed from the gastrointestinal tract, and that the renal excretion of the drug accounts for very little of the daily dose. It may be concluded from these facts, and the fact that the plasma concentration becomes stabilized after several days of continued administration at constant dosage (see Figure 2), that the drug is mainly disposed of by the body by processes which result in its degradation.

Data which define the distribution of quinacrine in the blood are shown in Table II. The concentration of the drug in plasma, erythrocytes and leukocytes is in the order of 1, to 1, to 100-200. This excessive localization of quinacrine in the leukocytes acquires special importance in studies which would assay the inherent antimalarial activity of the drug, or would delineate the factors concerned with its physiological disposition. Its concentration in whole blood at any time during a period of therapy is dependent as much or more upon the leukocyte count as upon the underlying chemotherapeutically active concentration in the plasma. It may be noted in passing that the major portion of quinacrine in the plasma is bound to the non-diffusible constituents in the plasma,

TABLE III

DISTRIBUTION OF QUINACRINE IN THE TISSUES OF A DOG

The dog received a daily dose of 20 mg. per kilogram of quinacrine dihydrochloride daily for a period of 14 days prior to the experiment. The last dose was given 14 hours before the animal was sacrificed (wt. 10.0 k.).

	Quinacrine Concentration (mgm./kg.)
Plasma	0.061
Muscle	55.0
Lung	310.0
Spleen	571.0
Liver	1306.0

presumably the plasma albumin. It would, perhaps, be more precise were studies of the physiological disposition of quinacrine, together with studies on its chemotherapeutic activity, related to the concentration of unbound drug in plasma water. However, this appears to be an unnecessary refinement at the moment.

The distribution of quinacrine in the body as a whole is described in outline form by the data in Table III. These data, collected in experiments on the dog, indicate that the drug may achieve concentrations in the liver and spleen as high as 10,000-20,000 times those concurrently observed in the plasma. A similar situation obtains in the human, as evidenced by experiments which derive the same type of information through indirect means. Thus, a major portion of the administered quinacrine is localized in the tissues of the body, leaving little in the plasma to exert a chemotherapeutic effect. It is in consequence of this that large initial doses of the drug must be given if one is to expect a high initial plasma drug concentration and an abrupt therapeutic effect. Furthermore, the extensive localization, together with the low rates of degradation (established by other types of experiments) and renal excretion, lead to a low rate of decline of the plasma quinacrine concentration, and consequently a low rate of the loss of the protection conferred by quinacrine, subsequent to the termination of drug administration.

*Antimalarial activity:** The response of well standardized and rigidly controlled blood induced vivax and falciparum malaria to various plasma levels of quinacrine has been utilized to assay the inherent antimalarial activity of the drug in terms of its ability to terminate or suppress the clinical attack. Blood induced malaria is best suited for such a study since it has the advantage of making available the simple erythrocytic phase of the disease.

It has been found in such infections that the P. vivax parasites[9] are completely and permanently eradicated when plasma quinacrine levels of 30 micrograms per liter or more are maintained for not less than 4 days. Plasma quinacrine levels between 10 and 30 micrograms per liter generally produce temporary or partial effects and levels below 10 micrograms per liter produce little or no effect when maintained for a 4 day period. P. falciparum parasites[9] appear to be more resistant and require approximately 50 micrograms per liter maintained for a 6 day period for complete and permanent eradication of the infection.

Recent work has shown that the erythrocytic phase of a mosquito induced vivax malaria[9] has the same sensitivity to the chemotherapeutic activity of quinine as the blood induced infections detailed above. The figures just quoted, then, will have some significance when applied to naturally acquired malarias. Recent work[9] also substantiates the previous belief that there are strain differences in susceptibility to the antimalarial activity of quinine and these differences may be expected to extend in certain instances to the antimalarial activity of quinacrine and other agents. However, the differences observed are not sufficiently great that the regimens of therapy given below will not, in general, terminate clinical activity.

The correlation between oral dosage and plasma quinacrine levels is poor[6] so that it is difficult to state the antimalarial activity of the drug in terms of oral dosage. However, knowing the minimal plasma drug levels which are required to produce a given therapeutic effect and the range of plasma drug concentrations which are to be expected on a given dosage regimen in a group of individuals, it is possible to place the oral dosage sufficiently high for the maximal benefit to be derived from the drug for all but the exceptional individual.

* The blood induced and mosquito induced vivax malaria made use of specific strains of P. vivax which are purported to be offshoots of the McCoy strain. While it is certain this is the case with the mosquito induced infections, cross immunity experiments have not as yet satisfactorily demonstrated that this is the case for the strain utilized in the blood induced infections. The falciparum malarias were induced by the inoculation of blood infected with the MacClendon strain of P. falciparum.

*Dosage schedules:** It is with an understanding of these aspects of the physiological disposition and antimalarial activity of quinacrine that it is possible to establish rational regimens of therapy for both the suppression of the malarias and for the treatment of the clinical attack.

The primary end to be sought in the treatment of the clinical attack is an abrupt termination of the clinical manifestations of the infection. The lower curve in Figure 2 represents the mean daily plasma quinacrine concentration of a group of individuals who received 0.1 g. of quinacrine three times daily, a dosage schedule commonly recommended prior to 1943.[10] Very low plasma drug concentrations are achieved with such a regimen during the first two or three days of therapy because of the extensive localization of the drug in tissues. It is true that the plasma level increases progressively throughout the period of drug administration as more and more quinacrine accumulates in the tissue. However, because of the early low levels it is not to be expected that such a dosage will produce an early termination of clinical activity although, if continued for a period of days, plasma drug concentrations are achieved which will terminate the clinical attack. It is the delay in the initial effect of quinacrine, with such a dosage schedule, that led to the recommendation that quinacrine therapy be preceded by a 2 to 3 day course of quinine.[11]

The situation is quite different when doses of quinacrine totalling 0.8-1.0 g. are administered during the initial day of therapy. This may be done by either the oral route or by a combination of intramuscular and oral administration (Figure 2). High plasma drug concentrations are obtained with either of these regimens during the initial 24 hours and may be maintained with the serial administration of 0.1 g. three times daily thereafter. It is to be expected from such plasma drug curves that a therapeutic effect will be apparent very early during the course of drug administration and in fact, such has been found to be the case.

These principles may be translated into simple dosage schedules for the administration of quinacrine. It is advised, in the routine treatment of malaria, that 0.2 g. doses of quinacrine be given at the time of the diagnosis of malaria, and at 4 hour intervals until a total of 1.0 g. has been given. Thereafter, it should be continued at a dosage level of 0.1 g. three times daily for a total period of 7 days.

* The dosage schedules listed are calculated for adults.

More acutely ill patients, i.e., those with fulminating falciparum malaria, or those with nausea and vomiting, may be treated effectively through the use of intramuscular injections of quinacrine (Figure 2). It is not considered safe in either of these cases, to depend upon an exclusively oral route for the administration of drug. Very high and effective plasma drug concentrations are achieved within 15 minutes after the intramuscular injection of 0.4 g. of quinacrine dihydrochloride.[9] This is commonly given in two 0.2 g. intramuscular injections, one into each buttock. Subsequent therapy may then be by the oral route if possible, or by the intramuscular route until oral therapy can be substituted. When oral therapy is utilized, subsequent to an intramuscular injection, it is advised that 0.2 g. doses of quinacrine be administered at 4 hour intervals until a total of 1.0 g. has been given by a combination of the two routes. Thereafter, 0.1 g. is administered 3 times daily for a total period of 7 days. Should it be necessary to continue therapy by the intramuscular route, 0.2 g. may be administered at 8 hour intervals until a total of 1.0 g. has been administered, then at 12 hour intervals until it is possible to begin oral therapy with 0.1 g. three times daily.

It is to be emphasized that the indications for the intramuscular use of quinacrine are two, i.e., fulminating falciparum malaria, and clinical attacks of malaria in which the symptoms of nausea and vomiting are prominent. An additional word may be said in relation to the former of these two indications. Most clinicians in the past have used intramuscular or intravenous quinine in starting the treatment of fulminating falciparum malaria because it is known that this produces a rapid therapeutic effect. Intramuscular quinacrine has not been used to any great extent for such a purpose since it has not been appreciated that it may achieve an equally rapid effect. As noted above, very high and effective plasma quinacrine levels are found within 15 minutes of its intramuscular injection. The toxic hazard of intravenous injections of quinine is sufficiently great that it must be given slowly so that no advantage, with respect to time, is gained with the intravenous use of quinine as compared to the intramuscular use of quinacrine. The latter procedure has the additional advantage of simplicity.

Any one of the recommended regimens will produce plasma quinacrine levels in excess of those required to eradicate the trophozoites and effect an abrupt termination of clinical activity in any of the malarias

in all but the exceptional individual. It is unusual for a patient to experience more than one subsequent paroxysm following the initiation of quinacrine therapy, providing adequate doses of the drug are administered.[9] A cure of the disease is to be expected in the majority of patients with falciparum malaria, but not in the patients with vivax malaria. Most of the latter will experience a recurrence of clinical activity within one to 12 months. The number of such relapses which are experienced before the infection is cured is dependent upon many factors which will not be discussed at this time.

The use of quinacrine for the suppression of the malarias will not be discussed in detail since this is not a common problem for civilian practitioners of medicine in temperate climates. However, it should be appreciated that clinical malaria may be suppressed in all but a small proportion of individuals during months of exposure to malaria by the weekly administration of 0.6 to 0.7 g. of quinacrine. This dosage, in most individuals, will result in plasma quinacrine levels known to have significant action on the erythrocytic phase of the malarias. Unpleasant gastrointestinal reactions were encountered when quinacrine was administered in the earlier recommended doses of 0.2 g. twice weekly.[10,11] However, these reactions are minimized and a therapeutic advantage gained when a larger total weekly dosage is administered in small daily doses of 0.1 g. given after meals. Suppressive therapy of this type is commonly continued for a three-week period after the last exposure to malaria. This may be expected to accomplish cures of the suppressed falciparum malaria, but not of the suppressed vivax malaria. Clinical activity due to the latter will appear in most infected individuals within a few weeks to some moths later. The time elapsing apparently depends upon many factors not well defined, among which are included the strain of the offending organism, and perhaps the number of strains involved in the infection, together with the density of the underlying tissue phase of the infection.

The delayed primary attacks which occur when clinical activity is suppressed at the time of the expected initial attack, as well as the clinical relapses, may be treated in much the same fashion as has been described above for the primary attacks. In general, the relapses or recrudescences of clinical activity respond more quickly to treatment than the primary attack, due to presence of some acquired immunity.

Some consideration must be given to the individuals who, subsequent

to an extensive exposure, develop vivax malaria which is characterized by innumerable relapses occurring at short intervals. These patients do well when maintained on suppressive therapy for a period of several months, perhaps six, following the treatment of any given acute attack. Actually, there is little information on the ultimate effect of this type of continuation therapy. Its rationale depends upon the assumption that the tissue phases of the plasmodium must progress through their normal life expectancy and that this will take place whether the erythrocytic phase of the disease and its accompanying clinical symptoms are, or are not, suppressed. The suppression of the erythrocytic phase of the disease permits an individual to pursue a normal life during the infection and should not, per se, prolong the course of the disease.

Quinine and the Cinchona Alkaloids

It is not necessary to spend much time in a discussion of the use of quinine, the cinchona alkaloids or totaquine, in the treatment of malaria, since it is unlikely that any of these preparations will be used extensively by physicians in this community. It is important to appreciate that any one of these may be utilized for the same purposes as have been described above for quinacrine. Recent work has confirmed the belief that the cinchona alkaloids other than quinine, i.e., cinchonine, cinchonidine and quinidine, have an antimalarial activity which is roughly the equivalent of quinine.[9] It is to be expected that the combination of these alkaloids in the form of a standard product such as Totaquine, USP, will also have roughly the same antimalarial activity as quinine. The dosage of totaquine as compared to quinine should be based on the alkaloid content of the preparation used.

The use of the cinchona alkaloids in the suppression and treatment of malaria differs from the use advised in the case of quinacrine, largely because the cinchona alkaloids are not localized as extensively in the tissues. However, the less extensive localization, together with more rapid rates of excretion and degradation, results in a rapid fall in plasma levels of the cinchona alkaloids when oral dosage is stopped. Consequently, relatively lower initial doses, as compared to the maintenance doses, are required to produce the desired result.

Quinine, of course, is a highly effective antimalarial agent. However, its antimalarial activity is less than that of quinacrine when the latter is properly used.[8] It was noted above that the effective 4 day plasma

concentration of quinacrine for vivax malaria due to a well standardized strain of P. vivax is 30 micrograms per liter. The effective quinine level, determined in the same way and on the same strain, is found to be 5 mgm. per liter. Inherently, i.e., based on the plasma concentrations required to produce a given therapeutic effect, quinacrine is almost two hundred times more active than quinine. The pharmacology of the two drugs, however, is such that, relative to the oral dose, lower plasma levels are achieved with quinacrine than with quinine. But still, the required oral maintenance dosage of quinacrine is considerably less than that of quinine. In addition, quinacrine plasma levels that are many times in excess of those required for an adequate therapeutic effect may be achieved without particularly toxic hazard, while the margin of safety with quinine is somewhat less.

The maximal benefit to be derived from quinine, in the treatment of the clinical attack, should be obtained by the administration of 3 grams of one or another of the available salts of quinine during the initial day of therapy, followed by 2 g. daily in divided doses. Therapy may be limited to a 7 day period in vivax malaria, and perhaps to a 10 day period in quartan and falciparum malaria. Patients with fulminating falciparum malaria, or those in whom nausea and vomiting are prominent symptoms, can receive quinine intravenously during the initial stage of therapy. This is commonly administered by slow intravenous infusions, single doses not to exceed 0.5 g., total dosage to be administered each day being the same as that advised for oral therapy. Again, oral should supplant parenteral therapy at the earliest possible time. The intramuscular use of quinine is contraindicated because of the not uncommon occurrence of necrosis at the site of the injection.

For suppressive purposes, it is necessary to administer as much as 1 g. of a quinine salt daily to approach a therapeutic result which is comparable to that which obtains when 0.1 g. of quinacrine is administered daily. Unpleasant side reactions are to be expected in a fair proportion of individuals carried on such a dosage regimen for any length of time. In addition it is less certain that suppressive quinine, used in accordance with these directions, will effect cures of the suppressed falciparum malaria. Consequently there would appear to be little question that quinacrine is the drug of choice, among those now available, when a suppressive therapeutic effect is desired.

Plasmoquin

Plasmoquin is advised in only one instance, i.e., to render a patient with falciparum malaria non-infectious to mosquitoes. It is commonly advised that plasmoquin be administered at a dosage of 10 mg. three times daily for a total period of 5 days.[3] However, such a regimen may be expected to produce toxic symptoms in a proportion of individuals and the consequence of such reactions may be serious. These may include the development of methemoglobinemia and moderate to severe disturbances of the gastrointestinal tract. However, the most serious toxic hazards are those which follow the occurrence of intravascular hemolysis. These reactions usually do not appear until the 4th or 5th day and therapy may be limited to three days without sacrificing the therapeutic benefit which is to be derived from plasmoquin administration.

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CARDIAC ENLARGEMENT ITS RECOGNITION AND SIGNIFICANCE

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IT HAS long been an accepted aphorism that an enlarged heart is a diseased heart. It might be well to preface our discussion with a few brief remarks as to why enlargement of the heart is unfavorable to the body economy. The physiologically dilated or hypertrophied heart may function with mechanical efficiency but it is important to recognize that the true measure of cardiac, or more properly circulatory, efficiency is the energy expenditure of the heart in maintaining its circulatory output, and not merely the ratio of the oxygen consumption to the kilogram-meters of actual work performed.[1] This distinction, i.e., the concept of efficiency of the circulation versus the mechanical efficiency of the heart muscle, is important for it helps to explain why cardiac enlargement betokens impaired reserve. Work expended against increased arterial resistance or to compensate for valvular defects is wasted in so far as the function of the heart to maintain its cardiac output is concerned. Since oxygen consumption is proportional to fiber length, or diastolic volume, the cardiac output is maintained by the dilated or hypertrophied heart with greater energy expenditure, hence efficiency is decreased. Hypertrophy and dilatation as a rule are closely associated so that when the heart is enlarged, some degree of dilatation of the cardiac chambers is usually present.

Beyond indicating the presence of disease the recognition of cardiac enlargement provides valuable information as to the type and the extent of the lesion; for characteristic changes frequently occur in various types of heart disease. Accurate estimation of the size of the heart, therefore, is most important.

Methods for studying the size of the heart include physical examination and techniques employing the Roentgen ray and the electrocardiograph.

* Presented at the Annual Meeting of the New York Heart Association at The New York Academy of Medicine, January 26, 1945.

It is with no intent to depreciate the importance of physical examination that we point out that there are serious limitations to inspection, palpation and percussion, particularly when the chest wall is muscular or obese, or in the presence of pendulous breasts or emphysema. Enlargement of the cardiac chambers other than the left ventricle cannot be detected on physical examination except in advanced stages.

It has long been recognized that characteristic electrocardiographic patterns occur with enlargement of the various chambers, but this aspect of electrocardiography has received relatively little attention. Recently we conducted a study to establish specific electrocardiographic criteria of left ventricular hypertrophy[2] and we found, employing these criteria, that the electrocardiogram provides the most sensitive method for detecting hypertrophy of the left ventricle, frequently exhibiting definite abnormal patterns where the roentgenologic findings are normal. Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following changes:

1. Increase in amplitude of the Q.R.S. complex, best expressed by the sum of R_1 and S_3. Hypertrophy is present if this sum exceeds 2.5 millivolts and is probably present if it is over 2.2 millivolts. The increase in voltage is the earliest electrocardiographic change in hypertrophy.

2. Any perceptible depression of the S-T segment in lead 1, even of as slight degree as 0.5 mm. (0.05 millivolts).

3. Lowering of T_1 below 1 mm. or further degrees of abnormality of T_1.

The changes in the S-T segment and the T wave may develop in the absence of left axis deviation, and left axis deviation is not an invariable or necessarily integral part of the electrocardiographic pattern of left ventricular hypertrophy. We found that the usual occurrence of left axis deviation in hypertension is due largely to a transverse position of the heart, which in itself causes left axis deviation. In slender subjects with left ventricular hypertrophy left axis deviation is not so often observed.

In advanced stages of hypertensive heart disease the characteristic electrocardiographic pattern approaching left bundle branch block is often observed. It must be emphasized that this is a late phenomenon and that employment of criteria such as we have proposed makes it possible to recognize left ventricular hypertrophy in its incipient stages.

The electrocardiographic patterns of left ventricular hypertrophy are of considerable prognostic importance. Thus, in a recent mortality study in hypertension[3] we found that there was a distinct increase in mortality with progression in the electrocardiogram toward an abnormal pattern. The life expectancy among those with the pattern of left ventricular hypertrophy was about half that of subjects with identical blood pressure readings in whom the electrocardiograms were normal.

A characteristic electrocardiographic pattern occurs with hypertrophy of the right as well as of the left ventricle. The changes consist of right axis deviation, accompanied by depression of the S-T segment in lead 3 and frequently lead 2, and inversion of the T wave in lead 3 and eventually in lead 2 as well. The voltage of the Q.R.S. complex is not regularly increased as it is with left ventricular hypertrophy. When the pattern is fully developed it is quite characteristic of right ventricular hypertrophy, but frequently in the less advanced stages it may be difficult to be certain that right ventricular strain is present because similar changes may occur in normal subjects of slender build, or as a result of positional changes of the heart.

Auricular enlargement, also, may be revealed in the electrocardiogram. The left auricle is the one which is usually enlarged, most often because of mitral stenosis. Changes occur in the P wave as a result of impaired conduction through the dilated and hypertrophied auricle. The P wave becomes notched, its duration exceeds 0.10 seconds, and it increases in amplitude to more than 0.25 millivolts. Ultimately, auricular fibrillation ensues as a result of longstanding auricular enlargement. Auricular premature beats and auricular flutter occasionally presage the change to auricular fibrillation.

Although hypertrophy of the left ventricle may often be detected earlier in the electrocardiogram, roentgenologic methods are superior in revealing auricular and right ventricular enlargement. When generalized cardiac enlargement is present the electrocardiographic changes are less specific, and the opposite effects of right and left ventricular enlargement may balance each other so that there is no deviation of the electrical axis, although other abnormalities, such as increased voltage and changes in the S-T segment and T waves tend to persist. The electrocardiogram may be relatively normal when enlargement is caused by dilatation of the cardiac chambers rather than by hypertrophy. Roentgenograms, therefore, are superior when generalized enlargement exists.

Roentgenologic methods for the recognition of cardiac enlargement include fluoroscopy, orthodiagraphy and teleoroentgenography.

Fluoroscopy, technically the simplest of roentgenologic procedures, as well as the most generally available, provides the greatest information and should be carried out routinely as a preliminary to further roentgenologic study. In any study of the size of the heart an attempt should be made to describe enlargement in terms of the individual chambers, for characteristic changes occur in various types of heart disease. For this purpose fluoroscopy is of particular advantage because the contours of the separate chambers may be inspected in their entirety by rotating the subject into oblique positions, and their limits ascertained by observation of the pulsations. Adequate visualization of all the chambers is afforded by making roentgenograms in the posteroanterior, left anterior oblique (50° to 55°), and right anterior oblique (50° or over), or right lateral, position. Examination in the latter view is aided by outlining (not filling!) the esophagus with a thick barium mixture, for the esophagus is in close relation to the posterior surface of the heart, particularly the left atrium. The relation of the chambers of the heart to adjacent mediastinal structures, such as the esophagus, bronchi, and chest parietes, which can be ascertained by study in the oblique positions, is of great value in establishing whether or not enlargement is present. Thus, early enlargement of the left atrium is indicated by indentation and retrodisplacement of the esophagus, and also by upward extension of the left atrial contour toward the left main bronchus, obliterating the infrabronchial space.[4] Eventually, the left bronchus becomes elevated and even compressed, but this is a later sign. The right ventricle forms the anterior surface of the heart, and, when it is enlarged, extends forward toward the anterior chest wall, narrowing the precardiac space; this is best revealed by study in oblique positions. Enlargement of the right ventricle is indicated indirectly in the frontal view by prominence of the upper left and of the right heart borders.

Fluoroscopy is not well suited for absolute measurement of the heart size since there is considerable magnification of the heart image due to divergence of the x-ray beam resulting from the short tube-film distance usually employed in fluoroscopic examination. The degree of magnification depends, not only on the tube-film distance, but on the object-film distance, as well. Magnification is, accordingly, greater in subjects with deep chests, in whom the heart contours are further removed from

the film, than in slender subjects and children.

Magnification can be obviated on fluoroscopy or in roentgenograms by a simple procedure.[5] A lead scale placed vertically parallel to the cassette alongside the subject in the plane of the anterior axillary line is magnified exactly in the same proportion as is the heart silhouette. The scale is recorded with the heart in the same exposure of the fluoroscopic screen or roentgenogram and serves as a reference scale for measurement of the heart size. This procedure is equally suitable for 35 mm. or 4″ x 5″ photographs of the fluoroscopic image, a technique which is being increasingly employed, particularly in surveys in the armed forces and industry.

Projection distortion of the heart in fluoroscopy also may be obviated by the orthodiagraphic technique. Only the central ray of the fluoroscopic beam, whose position is indicated by a small lead marker, is used to trace the outline of the cardiac contour. The screen and patient being fixed, the central ray is moved along the cardiac contour by moving the tube with the left hand, while the right hand follows the lead marker along the heart border recording numerous points at about one centimeter intervals. Orthodiagraphy requires training and exact application and does not appear to possess any advantage over the simpler lead scale method we have described which may be applied conveniently during fluoroscopy to obtain exact measurements of the cardiac shadow.

Roentgenography possesses the advantage over fluoroscopic techniques of providing an objective and permanent record, not only of the heart, but of the pulmonary fields as well, which are of interest and importance in the diagnosis of heart disease. At two meter (6.5 feet) tube-film distance (teleoroentgenography) the magnification of the cardiac image due to divergence of the x-ray beam is reduced to the order of 5 per cent; this does not increase appreciably until the tube-film distance becomes less than 150 cm. (5 feet).

Apart from the projection distortion there are numerous other pitfalls in interpretation of roentgenograms of the heart. The size, shape and position of the heart are influenced by certain physiological variables and technical considerations, which should be appreciated before deciding whether the heart is pathologically enlarged. It is important that the subject be centered properly, which can be recognized in the roentgenogram by an equidistance of the inner borders of the clavicle

from the midpoint of the vertebral spine. The tube should be at the level of the third anterior intercostal space. Even slight degrees of rotation may significantly alter the size of the cardiovascular shadow, particularly the aortic arch silhouette. The exposure should be made in the erect or sitting position, and with respiration suspended in ordinary inspiration since extremes of respiration or straining may cause marked variations in the size of the heart. The size of the cardiac shadow varies considerably depending on the phase of the cardiac cycle in which the exposure is made. When the pulsations are vigorous the transverse diameter of the heart may vary by as much as 1.5 to 2 centimeters from systole to diastole. Since diastole is longer than systole at ordinary heart rates, roentgenograms are more often exposed in diastole. It is not true as is widely supposed that a full second exposure lasting through a complete cardiac cycle will record the diastolic or largest heart shadow.[6] It has been shown, in fact, that the border of the heart in long exposures lasting through the complete cardiac cycle more closely approximates the systolic, or smallest, heart size. Prolonged exposures thus serve no advantage and not only give an indistinct cardiac outline but blurred hilar structures as well due to transmitted motion from the cardiac pulsations. Several devices employing pulse waves, heart sounds, and the electrocardiogram have been contrived to permit exposure at selected phases in the cardiac cycle. The technique of roentgenkymography makes it possible to register one or several complete cardiac cycles on a single film and provides a record of the cardiac outline both in systole and diastole.[7]

Several anatomical peculiarities may cause confusion in interpreting the cardiac shadow. The most important is an extra-pericardial fat pad which merges with the lower left heart border and which may obscure the apex. The margin of the fat pad must not be mistaken for the left heart border which may be discerned within the fat pad, particularly if the roentgenogram is made with slightly over-penetrated technique. Skeletal abnormalities of the thorax, such as funnel chest and kyphoscoliosis, by displacing and distorting the heart occasionally may render difficult the accurate determination of the size of the heart. The dextroscoliotic spine may simulate the right heart border or ascending arch of the aorta, and a diagnosis of cardiac enlargement or dilatation of the aorta may thereby be made erroneously. The size, shape and particularly position of the heart may be altered in pulmonary diseases

such as fibroid phthisis, atelectasis, pneumothorax, etc.; and by diaphragmatic hernia or elevation of the diaphragm as in pregnancy and ascites.

Several measurements such as those of Vaquez[8] and Fray[9] have been proposed which purport to serve as criteria for enlargement of the individual heart chambers. The value of such measurements is, at best, limited. Attempts to measure the cardiac chambers separately are necessarily inexact since only one border is visualized, the shadows of the various chambers merging to form the cardiac silhouette. The relation of the heart to adjacent structures, such as the esophagus, bronchi and thoracic parietes, determined by fluoroscopy and teleoroentgenogram study in posteroanterior and oblique positions as already indicated, is of greater value than mensuration in detecting enlargement of the individual chambers.

Measurements are of greater value as an index of generalized enlargement of the heart than in determining the size of the individual chambers. There is a definite field of usefulness for measurement standards in evaluating enlargement of the heart as a whole since very often enlargement does not involve individual chambers distinctly and one can state only that the heart is enlarged. Mensuration is unnecessary when gross enlargement exists, but lesser degrees of enlargement often escape detection on inspection. Conversely, an apparently large cardiac shadow may assume less significance when it is considered in relation to standards of body build. If proper account is taken of the physiological variables which influence the size of the heart, mensuration is a valuable aid in determining whether the heart is enlarged. Measurement is helpful also in comparison of changes in heart size in serial examinations in the same subject. Another field where measurement has found wide application is in physiological and pharmacological investigations of the heart.

Several physiological factors may influence the size of the heart and these must be recognized and considered in evaluating measurements. Body build has a most important determining influence on the size of the heart. The correlation of heart size with various factors, such as weight, height, surface area, muscular development, thoracic circumference and other thoracic measurements, etc., has been probed extensively. The dependence on weight is somewhat greater than on height but the correlation is improved if both weight and height are considered. A $\frac{\text{weight}}{\text{height}}$ index has been evolved which appears to serve as a

satisfactory coefficient for prediction of normal standards. The influence of sex, and of age in adults, on the size of the heart is relatively small compared with the factors of weight and height, and for practical purposes may be disregarded in prediction standards.

Of the many measurements that have been advocated the best known are the transverse, longitudinal and broad diameters. These few simple measurements suffice to determine whether the heart is enlarged. The transverse diameter, and the area of the frontal cardiac silhouette, which may be determined from the long and broad diameters, as we will presently show, are the most thoroughly tried and standardized and among the best of all measurements.[10] In addition, the heart volume, which is of great physiological interest, can be accurately calculated from these diameters.

The simplest, most widely employed, and one of the most useful measurements is the transverse diameter, which is the sum of the greatest extension of the right border to the right, and of the left border to the left, of the midline. The cardiothoracic ratio, which is predicated on the assumption that the transverse diameter should be less than half the transverse diameter of the chest at the level of the diaphragm, has been widely popularized, but is crude and inexact. The width of the thorax is only a rough index of body stature, and is altered in any given case by respiration, and also in pathologic conditions, such as emphysema. Ordinarily the transverse diameter of the heart is considerably less than half the transverse diameter of the chest, so that appreciable enlargement may escape detection if this ratio is employed as an index of the size of the heart. More accurate standards, based on weight and height have been established both for the orthodiagram by Hodges and Eyster[11] and for the teleoroentgenogram by Ungerleider and Clark.[12] Teleoroentgenographic standards are slightly greater than those for the orthodiagram, so that it is not proper to use the orthodiagram values in reading teleoroentgenograms. Because of the increasing employment of the teleoroentgenogram, a new prediction table, based on a study of 1,460 teleoroentgenograms of normal subjects, was prepared, and this should be employed, rather than the older orthodiagram standards, when reading teleoroentgenograms.

The actual transverse diameter should not be interpreted too strictly in relation to the predicted value, for there are appreciable physiologic variations in the size of the cardiac shadow in addition to changes due

to the phase of the heart cycle and respiration. Diameters which are more than 10 per cent above the predicted value should be regarded as abnormal, and the heart may be considered as almost certainly enlarged if the transverse diameter is over 15 per cent in excess of the predicted diameter, since less than three per cent of normals exceed this limit. An increase in the transverse diameter is most often caused by enlargement of the left ventricle, but enlargement of any of the cardiac chambers, even of the left auricle, when it forms the right border of the heart, can widen the transverse diameter.

The utility of the transverse diameter employing our tables has been confirmed in several studies. The conclusion of Comeau and White in their article entitled A Critical Analysis of Standard Methods of Estimating Heart Size from Roentgen Measurements,[13] may be quoted.

> "1. A comparison of transverse heart diameters, frontal cardiac area, and heart volumes in 200 normal hearts leads us to conclude that the transverse diameter of the heart compares favorably with the other actual heart measurements and is the most satisfactory from the clinical standpoint.
>
> 2. We believe that the cardiothoracic ratio is not sufficiently reliable to warrant the wide usage which it now enjoys and that it should be discarded in view of the fact that it has been superseded by a more accurate and an equally simple correlative method.
>
> 3. We have found that the prediction tables offer the best approach to the problem of determining whether cardiac enlargement exists in an individual case. Our results indicate that the use of the transverse heart diameter and its deviations from the predicted normal is as yet the most reliable and the most applicable clinically of the existent methods."

Recently an important study was carried out by Sherman and Ducey[14] in which a direct comparison was made between the weights of the heart at autopsy in 200 adult males, and three types of measurement; the Ungerleider and Clark transverse diameter prediction table, the Newcomer heart-lung rectangle method and the cardiothoracic ratio. Their findings were reported as follows:

> "The values obtained by the Ungerleider method more closely approximate the enlargement by weight than do those by the other two methods, particularly in borderline cases. The Ungerleider method is the only one of the three by which enlargement of 40

per cent or less can be detected. There is constant correlation between the percentage deviation of the transverse diameter, as obtained by the Ungerleider method, and the percentage deviation in heart weight."

Two other diameters, the long and broad diameters, are well known, although these are somewhat less valuable individually than the transverse diameter. The long diameter extends from the junction of the cardiac and vascular silhouette on the upper part of the right border of the heart obliquely downward to the apex on the left. This diameter, which is approximately ten per cent greater than the transverse diameter, is increased chiefly as a result of left ventricular enlargement. The broad diameter is the greatest diameter perpendicular to the long diameter. The broad diameter is often drawn as the sum of the two perpendiculars from the long diameter to the lower right and upper left heart borders, but properly it is the greatest single diameter from upper left to lower right heart border perpendicular to the long diameter. If the heart is placed transversely, it may be necessary to extend the lower part of the right border slightly below the diaphragm in its natural curve in order to delineate the limit of the broad diameter. The broad diameter averages about 15 per cent less than the transverse diameter.

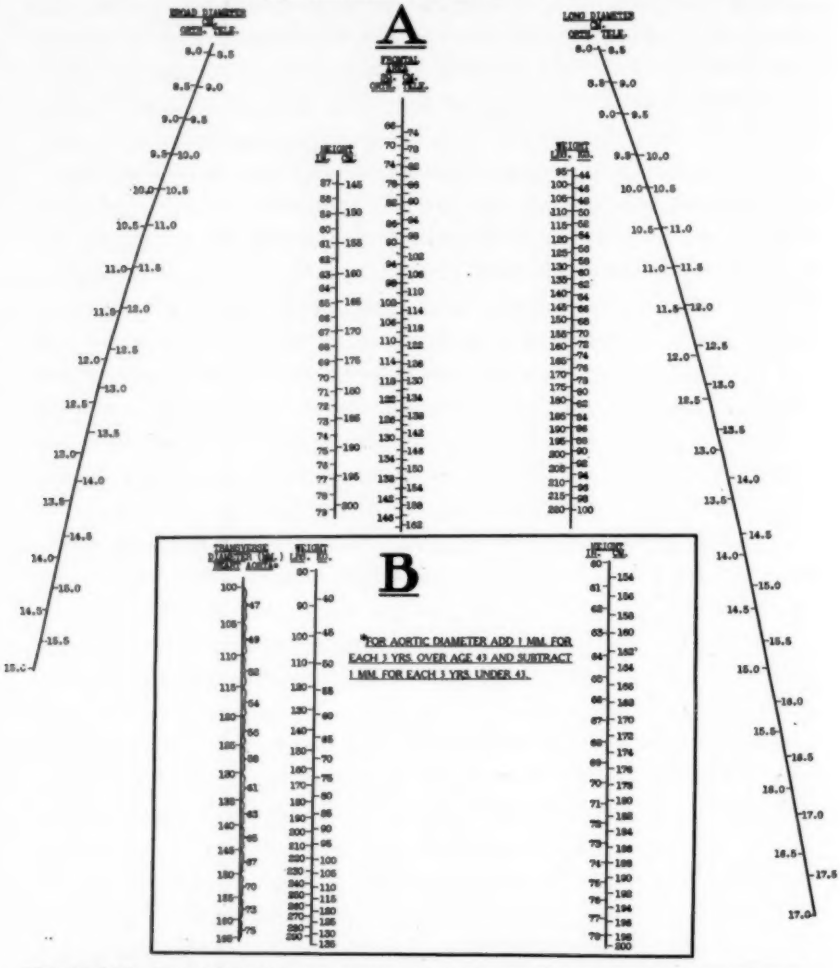
The long and broad diameters are of interest, not so much by themselves, but for their product, i.e., the frontal cardiac area, which is an expression of the two-dimensional size of the cardiac shadow.

The area of the frontal cardiac silhouette in relation to standards based on weight and height has been widely recommended as an excellent criterion of the size of the heart. In order to ascertain the area of the frontal silhouette, the upper and lower limits of the heart shadow must be completed by arbitrary and imaginary lines, and this requires considerable experience to attain duplicable results. The area is measured by means of a planimeter, or by counting squares within the area on cross-section paper. In orthodiagraphic examination, observation of the pulsations helps in outlining the upper and lower limits of the heart contour. In the teleoroentgenogram, however, the error in completing the upper and lower borders is much greater, and, for this reason, satisfactory frontal area measurements have not hitherto been obtained from the teleoroentgenogram, although this method yields excellent results in orthodiagraphy in the hands of those who are well trained in the technique. Inasmuch as the cardiac shadow is ellipsoid in shape, its area may

Nomograms for Area and Transverse Diameter of frontal heart silhouette

A. PREDICTED AREA FROM WEIGHT AND HEIGHT[1], AND ACTUAL AREA FROM LONG AND BROAD DIAMETERS ($A = \frac{\pi}{4} L \times B$), FOR ORTHODIAGRAM AND TELEOROENTGENOGRAM.

B. TRANSVERSE DIAMETER OF HEART[2] AND AORTIC SILHOUETTE[3] PREDICTED FROM WEIGHT AND HEIGHT, FOR TELEOROENTGENOGRAM



THE VALUES FOR ACTUAL (OR PREDICTED) AREA ARE READ AT THE POINT AT WHICH A STRAIGHT LINE EXTENDING FROM THE LONG AND BROAD DIAMETERS (OR WEIGHT AND HEIGHT) INTERSECTS THE CARDIAC AREA SCALE. ORTHODIAGRAM VALUES ARE ON THE LEFT, TELEOROENTGENOGRAM VALUES ON THE RIGHT. IN THE LOWER NOMOGRAM THE PREDICTED TRANSVERSE DIAMETER OF THE HEART (LEFT SIDE OF SCALE) OR AORTIC ARCH (RIGHT SIDE OF SCALE) IS OBTAINED AS AN EXTENSION OF A STRAIGHT LINE CONNECTING HEIGHT AND WEIGHT. A CORRECTION FOR AGE, AS INDICATED, IS NECESSARY FOR THE AORTIC DIAMETER.

FIGURE 1

be calculated from the product of its axial long and broad diameters (area of ellipse $= \frac{\pi}{4}$ long x broad diameters.) Calculation of the cardiac area by means of the formula, $\frac{\pi}{4}$ long x broad diameters, yields values which correspond very closely to the actual area, as measured by planimetry (within three per cent). This product may, therefore, be used to estimate the cardiac area in lieu of planimetry.[10] This is of particular advantage in the teleoroentgenogram because the long and broad diameters can be measured accurately, whereas the planimetric estimation of the cardiac area is less accurate. The product ⅔ long x transverse diameters, approximates the cardiac area, but is less satisfactory than the product of long and broad diameters, for the mean deviation from actual areas, as ascertained by planimetry in 134 orthodiagrams, was found to be seven per cent, whereas with the long and broad diameter product the mean deviation in the same group of 134 cases was less than three per cent. The actual cardiac area should not exceed ten per cent over the predicted value, and, if it does, the heart may be considered enlarged. Recently we prepared a nomogram for prediction of the cardiac area from weight and height, and actual area as calculated from the long and broad diameters (Figure 1). The nomogram permits the frontal area to be read directly without calculation from the long and broad diameter measurements. Predicted values for the frontal area based on weight and height are indicated in the same nomogram chart on another scale.

The validity and usefulness of the nomogram for frontal area has been confirmed by Kurtz[15] on the basis of 155 cases tested. Kurtz reported, "This relatively close approximation to the planimetric area indicates that the method has a practical application of distinct value in the great majority of cases." He states further, "Most cardiologists will admit that the cardiothoracic ratio is the poorest roentgenographic method of detecting cardiac enlargement, whereas orthodiascopic measurement of the frontal area of the cardiac silhouette is probably the most accurate. The latter has the obvious disadvantage of requiring a considerable amount of training in the technique. If the other disadvantages of measuring the frontal area, namely, the completing of the upper and lower borders and the use of a planimeter, could be obviated, one would have an ideal method for even the untrained. The method proposed by Ungerleider and Gubner approaches the ideal."

To summarize our discussion of cardiac measurements, it is evident that with the use of either or both the transverse diameter and the nomographic determination of frontal area, we have two simple and accurate methods, which suffice to determine whether cardiac enlargement is present.

Roentgenologic examination of the heart should invariably include observation of the aorta, for abnormalities such as widening, tortuosity, and calcification occur frequently in heart disease, particularly in hypertensive and arteriosclerotic heart disease and in syphilis. Measurement of the true caliber of the aorta is difficult because both contours are not visualized in the frontal position. The left border of the descending aortic arch is visualized in the frontal roentgenogram, and, if the esophagus is filled with barium, the right border of the aorta is indicated by the aortic indentation of the esophagus; therefore, the diameter at this level of the aorta can be ascertained by subtracting 2 mm. representing the thickness of the esophageal wall (Kreuzfuchs' method).[16] The method is not dependable when the aorta is tortuous and the aortic knob projects to the left. Where a portion of the aortic knob is distinct, as is usually the case in adults, the true diameter of the aorta at this level may be ascertained by the simple method we have proposed,[17] of completing the circle, of which the aortic knob is an arc, by means of a compass. The caliber of the aorta determined by this simple procedure checks exactly with the diameter obtained by visualization of the aorta in the left anterior oblique position and with the Kreuzfuchs' method. The diameter of the transverse arch of the aorta can frequently be measured directly in the left anterior oblique position, particularly when some degree of emphysema is present to aid contrast, or when overpenetration technique is employed. The diameter of the aorta at this level averages 3.0 to 3.5 cm. in adults, varying from 2 to 4 cm. depending on body build and age.

These methods indicate the size of the transverse and descending aortic arch, but it is the ascending aorta which is most often enlarged in disease. The first portion of the ascending aorta is buried in the cardiac shadow, and cannot be studied by any means except contrast visualization with diodrast. The diameter of the ascending aorta just above the aortic valve normally is 25 per cent greater than the diameter of the transverse arch at the level of the aortic knob. The ratio does not hold in pathological states as the ascending aorta usually becomes dilated to

a much greater degree than the transverse or descending arch. Enlargement of the ascending aorta is evidenced by prominence of the right border of the vascular pedicle and by a forward bulge of the anterior border of the aorta above the cardiac shadow as observed in the left anterior oblique views.

The right border of the vascular pedicle is formed by the superior vena cava in the majority of young subjects; in later life it is more frequently formed by the right border of the ascending aorta. An increase in the transverse diameter of the vascular pedicle in the frontal roentgenogram does not specifically indicate enlargement of the aorta, for this may result from tortuosity alone; however, this measurement is useful in that it does distinguish between a normal and abnormal aorta. In a recent study, it was found that the transverse aortic diameter in normal subjects is closely related to weight and height.[18] The table established for predicting the transverse diameter of the heart from weight and height may be employed equally well for the aortic arch diameter. A correction for age is necessary; 1 mm. is added for each three years over the age of 43, and subtracted for each three years under the age of 43. Deviations from the predicted value up to ten per cent are within allowable normal limits, but deviations in excess of this are infrequently seen, and the aorta may be considered as almost certainly abnormal if the diameter exceeds 15 per cent above the predicted value, for 92 per cent of normal subjects fall within this range. The transverse diameter of the aortic arch is a simple and valuable standard for measment of the aorta. It is important that the roentgenogram be made with the subject properly centered for even slight rotation into the oblique positions markedly alters the aortic arch transverse diameter. If the diameter is found to exceed normal values, further study in the left anterior oblique position is indicated for the aortic arch is best visualized in this view.

On the same nomogram chart employed for determining cardiac areas, we have, in the lower section included a nomogram for the predicted transverse diameter of the aortic arch and transverse diameter of the heart, based on our table. This nomogram chart, therefore, serves as a simple method for the application of all the measurements necessary, i.e., the transverse diameter of the heart, the frontal cardiac area, and the aortic arch transverse diameter.

We have devoted the greater part of this presentation to a discus-

sion of cardiac measurements and to certain phases of cardiac enlargement which have interested us, such as electrocardiographic changes, the lead scale method to replace orthodiascopy, obliteration of the infrabronchial space as a sign of left atrial enlargement, the arc method of determining the diameter of the aorta, and tables and nomograms for transverse diameter and frontal area. I do not wish to leave you with the impression, however, that the recognition of enlargement is the only important consideration in roentgenologic study of the heart. Time does not permit us to go into detail, but we have already briefly indicated that fluoroscopic study of the individual heart chambers is an invaluable aid in various types of heart disease. Observation of the cardiac pulsations also contributes such information, particularly in cardiac infarction, constrictive pericarditis and pericardial effusion. The cardiac pulsations may be analyzed objectively by means of roentgenkymography, a technique which has proven of value not only in clinical problems but in physiological studies as well, such as determination of cardiac output.[7] One of the really significant advances in cardiac roentgenology in the past few years has been the technique of contrast visualization of the cardiac chambers with diodrast, introduced by Robb and Steinberg.[19] The application of the method has been advanced notably with the multiple exposure method,[20] and has proven of particular value in the diagnosis of congenital cardiac lesions.[21]

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WILLIAM WORTHINGTON HERRICK
1879–1945

IN MEMORIAM

William Worthington Herrick

Dr. Herrick was, above all else, what Sir William Osler would have called a true physician, a doctor's doctor, the one chosen by his confreres as their consultant. Those of us who are left bereft by the suddenness of his passing are sustained by the thought that he had attained the highest honor his friends could give him—The Presidency of The New York Academy of Medicine.

William Worthington Herrick was born in a country parsonage in Sherman, Connecticut. His father was pastor of the church for sixteen years. Six of his great uncles had been doctors and when he was fifteen he made up his mind to be a physician. Three generations of Herricks had preceded him to Yale. Upon his office wall hang the Yale diplomas of his great-grandfather (1798); his grandfather (1822); his father (1871); his own (1902); and that of his son (1933). After graduating from the Yale Medical School with high honors in 1905, he spent the next two years as an interne at St. Luke's Hospital in New York where he worked in both the pathological and medical services.

At some time during these years of internship, he developed tuberculosis. It was a challenge to his medical science. He returned to the family home in Gaylordsville, Connecticut, and, as he often told the story, "rested on a cot out of doors and drank milk until he was cured." For a time after his recovery, he assisted the local doctor and thus got his first taste of private practice.

For the next four years Dr. Herrick was assistant to Drs. E. G. and Theodore Janeway in New York. At this time the teaching of medical students became of intense interest to him and from 1908 on he served successively as Instructor, Assistant, Associate, and then full Professor of Clinical Medicine at the College of Physicians and Surgeons of

Columbia University. From 1910 to 1929 he was Assistant Attending Physician at Roosevelt Hospital.

During World War I, Dr. Herrick served as a Major in the United States Army and was Chief of Medical Service at Base Hospital, Camp Jackson, S. C. Toward the end of the war he was medical consultant for the Southeastern Department.

During the present war he was a member of the Medical Advisory Board of Selective Service System of New York City and Chairman of the Physicians and Surgeons group of the American Red Cross War Fund for 1945.

His medical writings date from 1908 and scarcely a year passed without the publication of a carefully written paper upon the subject he was studying at the time. He was especially interested in the metabolic disorders, meningococcus meningitis, trichinosis, complications and toxemias of pregnancy, and later, in diseases of the heart and lungs. About 1924 he assumed the complete editorship of the Nelson Loose-Leaf Medicine and until his death was responsible for these many volumes.

In all his fields of endeavor, he gave evidence of his ability both as an organizer and executive. He drove himself hard. He expected nothing of his associates which he would not do himself. In his private practice, the younger men who have worked with him got invaluable training and experience by constant association with his expert wisdom and thoroughness, and then with his encouragement they branched out upon their own. To these younger doctors he was a rock upon which they leaned.

He said of himself that he had a single track mind—his objective being to further the cause of medicine through the training of the next generation of physicians.

To his patients he was a hope and a consolation. Each one who came to his office for diagnosis was a challenge to him. With infinite patience he would try to reach the correct solution of these complicated medical problems. That one of his special interests was in diagnosis was shown in his teaching and in a scholarly paper presented before the Practitioners Society on "A Consideration of Diagnosis including its Logistics."

Individual and social medical problems to him were never static. His address on assuming the Presidency of the Academy was entitled:

Scientific humanism in this changing world.

At the time of his death not only was he carrying the responsibilities of his private practice and The Academy of Medicine, he was attending physician at Presbyterian Hospital, vice president of Trudeau Sanatorium and Internist on the Medical Staff of the New York Central Railroad.

He was a member of the Board of Trustees of Sharon Hospital, Sharon, Connecticut and on the consulting staff there. He visualized the need for an enlarged and modernized hospital which would serve Sharon and the surrounding communities and he was working toward this accomplishment.

Dr. Herrick was a man of many resources. He was an inveterate reader; he enjoyed music and for relaxation played the pipe organ and the piano. During the summer he spent many hours in the work-shop of his Connecticut home, doing wood-carving and making reproductions of old furniture. He enjoyed long walks in the woods; he fished and played golf. His farm was a constant source of interest to him. He often said that everyone should have a piece of land to call his very own.

He died, as he would have wished to go, suddenly, without warning, at the height of his powers. He has left us the memory and example of a great man, admired, respected and loved not only for his professional attainments, but for his intellectual honesty and his personal integrity.

JOSEPHINE HEMINGWAY KENYON

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